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UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 C.F.R. § 1.53(b))

Attorney Docket No. AH0948Q
First Inventor or Application Identifier SHIH, et al
Title IMPROVED GROWTH STIMULANT COMPOSITIONS
Express Mail Label No. EL226882657US

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

1. ☒ Fee Transmittal Form (e.g., PTO/SB/17)
(Submit an original and a duplicate for fee processing)
2. ☒ Specification [Total Pages 22]
(preferred arrangement set forth below)
 - Descriptive title of the Invention
 - Cross References to Related Applications
 - Statement Regarding Fed sponsored R & D
 - Reference to Microfiche Appendix
 - Background of the Invention
 - Brief Summary of the Invention
 - Brief Description of the Drawings (if filed)
 - Detailed Description
 - Claim(s)
 - Abstract of the Disclosure
3. ☐ Drawing(s) (35 U.S.C. 113) [Total Sheets]
4. Oath or Declaration [Total Pages]
 - a. ☐ Newly executed (original or copy)
 - b. ☐ Copy from a prior application (37 C.F.R. § 1.63(d))
(for continuation/divisional with Box 16 completed)
 - i. ☐ DELETION OF INVENTOR(S)
Signed statement attached deleting
inventor(s) named in the prior application,
see 37 C.F.R. §§ 1.63(d)(2) and 1.33(b).

* NOTE FOR ITEMS 1 & 13: IN ORDER TO BE ENTITLED TO PAY SMALL ENTITY FEES, A SMALL ENTITY STATEMENT IS REQUIRED (37 C.F.R. § 1.27), EXCEPT IF ONE FILED IN A PRIOR APPLICATION IS RELIED UPON (37 C.F.R. § 1.28).

ADDRESS TO: Assistant Commissioner for Patents
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5. ☐ Microfiche Computer Program (Appendix)
6. Nucleotide and/or Amino Acid Sequence Submission
(if applicable, all necessary)
 - a. ☐ Computer Readable Copy
 - b. ☐ Paper Copy (identical to computer copy)
 - c. ☐ Statement verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

7. ☐ Assignment Papers (cover sheet & document(s))
8. ☐ 37 C.F.R. § 3.73(b) Statement ☐ Power of Attorney
(when there is an assignee)
9. ☐ English Translation Document (if applicable)
10. ☐ Information Disclosure Statement (IDS)/PTO-1449 ☐ Copies of IDS Citations
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Prior application information: Examiner Group / Art Unit:

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17. CORRESPONDENCE ADDRESS

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PATENT CASE AH0948Q
IMPROVED GROWTH STIMULANT COMPOSITIONS

FIELD OF THE INVENTION

5 The invention relates generally to veterinary pharmaceutical compositions and formulations that control the release of the active compound therein to the animal. More specifically, the present invention discloses actives in a dual formulation that stimulates growth and weight gain in domestic animals.

10

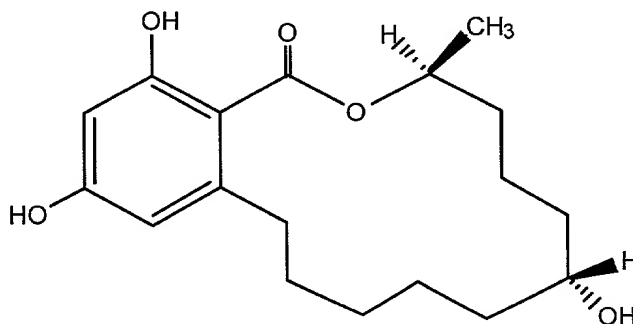
BACKGROUND OF THE INVENTION

 There have been many recent advances in the veterinary sciences and veterinary pharmacology that have resulted in the growth and development of larger, healthier and heartier, bovine, porcine, ovine and
15 equine species. Particularly with respect to the bovine, ovine and porcine groups, the need to feed the world's population through the production of meat provides the impetus to raise domestic animals that grow as quickly and as large as possible.

 Anabolic agents, are widely used to promote the growth of cattle and
20 other domestic animals and stimulated growth promotion is desirable among the cattle farmers because it maximizes both rate of weight gain and the absolute amount of weight gain per average amount of food consumed, which is termed feed efficiency. Generally, steroids are supplied to the animal in the form of a bio-degradable or non-
25 biodegradable, implantable, time release pellet(s) which is injected under the skin using an implant device. These have been proven to be successful; however, the animals may have to be implanted 2-4 times during their growth period.

The implant devices used for the subcutaneous delivery of these steroid pellets consist of a housing in the shape of a pistol with a handle, a hollow needle for injecting the pellet into the body of the animal located at the front side of the housing, and a push-rod. The push-rod can be slid
5 into this hollow needle and is supported in the housing so as to be displaceable longitudinally. A chamber is provided in the housing and is attached to the needle. A magazine containing the pellets is inserted and displaceable therein. A longitudinally displaceable press-back device (spring ejector) is arranged in the housing parallel to the push-rod and
10 hollow needle in the housing. The push-rod and press-back device are moved by a driving mechanism which is similarly provided in the housing and which can be set in motion by the operating lever (trigger) fastened to the handle. This engages the driving mechanism and press-back device via a toothed segment coupled with the operating lever and a toothed
15 wheel engaging the press-back device and push-rod. Such a device design is described, for example, in U.S. patent 5,514,101.

Zeranol (Formula I, CAS Registry Number: 26538-44-3) is an anabolic agent which has shown impressive results in the promotion



Formula I

20 of weight gain and growth in cattle. Zeranol, a resorcylic acid lactone derivative, has shown to be a positive influence on dynamic protein metabolism. However, during the growth and development of the cattle, current formulations containing zeranol or other such anabolic agent must be administered at least twice over the 170 day growth and development
25 period for optimal results. Obviously, this necessitates bringing cattle in

from the fields, reinjecting the implant and transporting them out again which is a laborious and time-consuming process.

It has been determined that zeranol and other anabolic agents provide the best growth and weight gain results when administered early on and throughout the animal's growth cycle. This would require a dual
5 immediate-release/sustained-release formulation which has been hereinbefore not possible.

United States Patent No. 5,643,595 to Lewis discloses and claims a delivery system for veterinary growth promotants consisting of a
10 biodegradable polymeric matrix that contains a steroid growth promotant and an antibiotic. The steroid growth promotant may consist of zeranol which is formulated within sustained-release microparticles consisting of homopolymers or copolymers of lactic and/or glycolic acid. Other biodegradable polymers used in the sustained-release formulations include
15 polycaprolactone, polydioxonene, polyorthoesters, polyanhydrides, waxes, casein and mixtures thereof.

United States Patent No. 5,427,796 also to Lewis discloses a method for increasing animal growth comprising the administration of an anabolic steroid such as zeranol in a biodegradable microparticle delivery
20 system that releases the drug in a multiphasic manner. Drug delivery duration allegedly lasts up to 200 days. The same polymers are used in Lewis's other patents noted above and below.

United States Patent Nos. 5,419,910 and 5,288,496 to Lewis also disclose and claim a microparticulate sustained-release delivery system for
25 promoting growth in animals. The microparticles are comprised of a biodegradable polymeric matrix such as poly-D,L-lactic acid, polyglycolic acid and the like. The microparticles separately encapsulate a steroid growth promotant and an antibiotic. Zeranol, among other anabolic steroids, is disclosed as one of the useful actives that result in increased
30 bulk weight and growth.

United States Patent No. 4,874,612 to Deasy discloses a multi-component implant for the sustained-release, long-term delivery of pharmaceutical agents to humans and animals for the treatment of vitamin deficiencies, hormone replacement therapy, cancer therapy, infection and

the like. Preferably, the biodegradable polymers comprising the implants are used to deliver animal growth promotants which contain anabolic steroids such as zeranol as well as their combinations. The matrix used to make the implants consists of lactic acid/glycolic acid copolymers.

5 United States Patent No. 4,191,741 to Hudson *et al* discloses and claims polymeric implants for the long-term sustained-release of anabolic agents to ruminant animals. The steroids can be administered alone or in combination, one of which is estradiol. Zeranol is not specifically disclosed as one of these agents.

10 In fact, the use of biodegradable particles for the long-term, sustained-release of anabolic steroids and other pharmaceutical actives is known in the art. See for example, United States Patent Nos. 4,683,288; 4,677,191; 4,675,189; 4,542,025; 4,530,840; 4,489,055 and 4,389,330.

15 Unfortunately, not all of the prior art delivery systems enable zeranol to be administered in a way that maximizes the growth and weight gain potential that exists. Whereas zeranol and other anabolic agents must be administered two to four times during the growth phase of the animal, it would be most advantageous to provide a formulation that need only be administered once.

20 It is an object of the present invention to provide an anabolic implant formulation for increased growth and weight gain significantly greater than that achieved by animals given other steroid therapies and those given none at all. It is a further object of the present invention to provide an anabolic implant formulation that is given only once during the growth
25 phase of the animal yet provides both immediate and sustained, long-term administration of the drug throughout the growth period for optimal growth and weight gain.

SUMMARY OF THE INVENTION

30 The above-noted objects and others are addressed by aspects of the present invention which provides a method and an anabolic implant formulation for stimulating increased rate of growth, greater amount of growth and greater feed efficiency in cattle. The inventive method comprises administering to the animal an implant composition (or implant

as is commonly called) which comprises: (i) an immediate-release formulation containing an anabolic agent, and (ii) a controlled-release formulation containing an anabolic agent with a controlled-release agent, wherein the immediate-release formulation and the controlled-release
5 formulation cooperate to effect the desired stimulation of growth and weight gain. The immediate-release formulation and the controlled-release formulation may be simultaneously administered, or one immediately followed by the other in quick succession in whichever order the administrator chooses, to the animal. Applicants have found that the
10 inventive method of administering a dual formulation surprisingly results in growth and weight gain in the animal much higher than when either formulation (i) or (ii) is implanted without the other.

The present invention further discloses a method of preparing the above-noted dual formulation, an anabolic implant composition comprising
15 a dual formulation, as well as a method for stimulating growth and weight gain in animals using such compositions.

DETAILED DESCRIPTION OF THE INVENTION

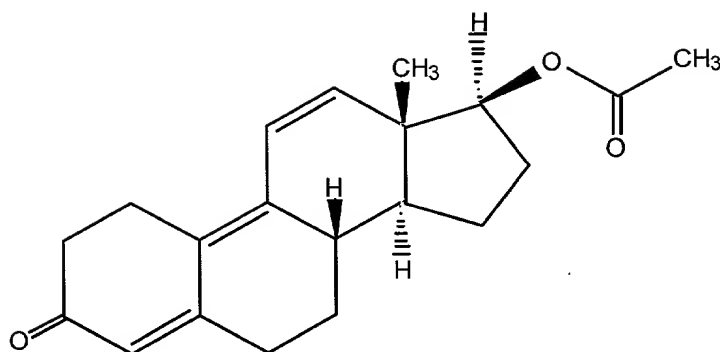
In one embodiment, this invention discloses a method for stimulating
20 increased rate of growth, greater amount of growth and greater feed efficiency in animals, sometimes generally referred to as cattle in this application. The method comprises administering an anabolic implant composition which is a dual formulation comprising (i) an immediate-release formulation containing an anabolic agent, and (ii) a controlled-
25 release formulation containing an anabolic agent and a controlled-release agent. The immediate-release formulation and the controlled-release formulation cooperate in the cattle to effect the desired stimulation of growth and weight gain. Even though the dual formulation may be administered as one composition by simultaneous administration of both
30 (i) and (ii) above in one administering (injecting) device, or administered one formulation followed by the other in quick succession in whichever order the administrator prefers, the following description, for simplicity sake, describes the invention as a single step simultaneous administration method.

The present invention concerns a method of stimulating increased rate of growth, greater amount of growth and greater feed efficiency in food animals which comprises providing to such animals biodegradable and non-biodegradable compressed tablets loaded with an anabolic agent.

- 5 The method of the present invention provides advantages over methods known in the art such as, *inter alia*, increased weight gain, a biodegradable or nonbiodegradable system, an implant system, the ability to mix tablets (pellets) containing different drugs and the ability to program the release rate (multiphasic release patterns).

- 10 In a preferred embodiment, administration of the growth promotant to food animals by the method of the invention is achieved by a single administration of the growth promotant loaded into compressed shapes such as, for example, tablets which release the active anabolic agent into the animal in a constant or pulsed manner and eliminates the need for
15 repetitive injections. Some of the tablets contain the active anabolic agent with no controlled-release agent, while the other tablets contain the active anabolic agent with a controlled-release agent, as described later in the **Examples**. Thus, the former acts as the immediate-release formulation while the latter acts as the controlled formulation.

- 20 The anabolic agent used in the two formulations may be the same or different. Illustrative anabolic agents suitable for and useful as growth promotants in the present invention include zeranol, estradiol and its derivatives such as, for example, estradiol benzoate, trenbolone acetate (Formula II, CAS Registry Number: 10161-34-9, available from Pharmacia
25 & Upjohn Company, Kalamazoo, Michigan), somatotrophin and its derivatives, testosterone and its derivatives such as, for example, testosterone propionate, salbutamol, progesterone, its derivatives and combinations thereof.



Formula II

In the immediate-release formulation, the anabolic agent may be used as it is or optionally formulated with minor amounts of other materials such as, for example, diluents, excipients, tableting agents and the like that are suitable for insertion under the skin. Examples of some of these materials include lactose as a diluent, magnesium stearate as a lubricant, silica as a glidant and the like. For example, the commercially available Ralgro[®] is formulated with lactose. Other diluent materials include, for example, mannitol, sorbitol, sucrose, dextrose, starches, hydrolyzed starches, and the like.

In the controlled-release formulation (also referred to as sustained-release formulation in this application), generally the controlled-release agent is a polymer matrix. The polymeric matrix material must be biocompatible. The term biocompatible is defined as a polymeric material which is not toxic to an animal and is not carcinogenic. Whereas the matrix material is biodegradable, the polymeric material should degrade by bodily processes to products readily disposable by the body and should not accumulate therein. When the matrix is non-biodegradable, it is still biocompatible and may remain within the animal at the site of implantation indefinitely. Suitable examples of polymeric matrix materials useful in the present invention include poly(D,L-lactide-co-glycolide) copolymer, ethyl cellulose, methyl acrylate-methyl methacrylate copolymer, methylcellulose, hydroxyethyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethyl cellulose, and the like. As in the immediate-release formulation, the anabolic agent and the polymer matrix material in the controlled-release formulation may be optionally formulated with minor

amounts of other materials such as, for example, diluents, excipients, tableting agents and the like, that are suitable for insertion under the skin. Examples of some of these materials include lactose as a diluent, magnesium stearate as a lubricant, silica as a glidant and the like.

5 The implant is generally in the shape of a cylindrical tablet. The tablet will generally have a diameter of from about 2.0 mm to 6.0 mm and a length of from about 1.0 mm to about 4.0 mm. The implants for the controlled-release are generally prepared by a procedure wherein the active anabolic agent is mixed with the poly(D,L-lactide-co-glycolide)
10 copolymer or the ethyl cellulose together with the other optional materials and this is then compressed in the die of a tableting press as is known in the art. Suitable illustrative procedures to make such implants with biodegradable polymer and with non-biodegradable polymer are described later in this application.

15 The rate of release of the anabolic agent in the controlled-release formulation can be controlled by a variety of measures. With respect to the poly(D,L-lactide-co-glycolide) copolymer, the rate of degradation of the carrier matrix can be increased by decreasing the size and consequently the molecular weight of the polymer chains. Increasing the amount of the
20 active anabolic agent and consequently reducing the active copolymer weight ratio will increase rate of release. The incorporation of additional plasticizers and other excipients may even speed up the degradation and release. Such modifications will be obvious to those skilled in the art.

 The preparation of the implants containing a biodegradable polymer
25 such as, for example, the poly(D,L-lactide-co-glycolide) copolymer, may be achieved utilizing any number of methods known in the art. An illustrative procedure is as follows. Preferably the anabolic active is first dissolved in a suitable solvent that will also solubilize, emulsify or disperse the poly(D,L-lactide-co-glycolide) copolymer. Suitable solvents include organic solvents
30 such as acetone, chloroform, methylene chloride, other aromatic hydrocarbons, cyclic ethers, esters, alcohols and the like and mixtures thereof. The polymer matrix material is also dissolved or dispersed in the solvent and the emulsion or solution formed thereby may be mixed into a

continuous phase. A surfactant may be added to the solution to prevent agglomeration.

5 The solvent is then removed, generally by the application of heat, the application of reduced pressure or both. The temperature employed is not critical but it should not be so high as to result in a degradation of either the active compound or the implant biodegradable matrix material. Once the solvent is removed, the solid dose implants may then be prepared using a standard tableting die press as is known in the art.

10 Preferably, the anabolic agent useful in the formulation of the present invention is zeranol. A commercially available formulation of zeranol is Ralgro[®] (from Schering-Plough Corporation, Terre Haute, Indiana) which additionally contains some lactose. The zeranol content in the present formulation is in an amount of from about 50 wt.% to 95 wt.% preferably from about 55 wt.% to about 85 wt.% and most preferably from
15 about 60 wt.% to about 80 wt.%, based on the total weight of the implant composition (including both the immediate-release part and the controlled-release part).

20 The poly (D,L,-lactide-co-glycolide) copolymer is incorporated in the sustained-release formulation in amounts ranging from about 1.0 wt.% to about 10 wt.% and preferably from about 1.0 wt.% to about 5.0 wt.%. If ethyl cellulose is used as the agent in place of the poly(D,L-lactide-co-glycolide) copolymer, greater amounts may be used such as from about 1.0 wt.% to 8.0 wt.% and preferably from about 2.0 wt.% to about 7.0 wt.%.

25 The other optional materials may be added to the formulation according to the length of drug delivery desired, but for the most part these will be added in standard amounts as is known in the art. For example, a diluent or excipient may be added in amounts of from about 20wt.% to 40 wt.%, preferably in an amount of from about 25wt.% to 40 wt.%, and typically in amounts of from about 25 wt.% to 30 wt.%. Coloring dyes for
30 foods, drugs & cosmetics ("FD & C"), and the like may be incorporated into the formulations in amounts of from 0.1 wt.% to 2.0 wt.% as is known in the art.

Implants containing non-biodegradable polymer such as, for example, ethyl cellulose, may be prepared by procedures known in the art.

An illustrative procedure is as follows: The anabolic agent such as zeranol is mixed with a diluent such as, for example, lactose, and optionally a suitable dye in a planetary mixer. In a separate mixer, an aqueous dispersion of ethylcellulose commercially available as Aquacoat ECD-30®

5 (available from FMC Corporation, Philadelphia, Pennsylvania) is mixed with a suitable plasticizer such as triacetin, or dibutyl sebacate, etc. The plasticized ethyl cellulose is then blended with the anabolic agent/lactose mixture and granulated. The granules are dried at a temperature of from about 50° c to 70° C until the formulation is characterized by a moisture
10 level of from about 0.2 wt.% - 0.6 wt.% based on the total weight of the formulation. The dried granules are then sized through a sieve, such as, for example, the Fitzmill sieve or its equivalent, and then lubricated with an appropriate lubricant such as magnesium stearate and a glidant such as, for example, silicon dioxide. The granules are then compressed into
15 pellets of the desired size and hardness.

Without being bound to any theory, it is believed that ethyl cellulose which is a pseudolatex matrix is distributed evenly throughout the wet mass. Upon drying, the matrix particles become finely blended with the active anabolic agent and the excipients. Compression in the tablet die
20 further condenses the ingredients together.

A heating or curing step is important as this seems to fuse or coalesce the ethyl cellulose particles forming a true matrix structure about the active. This results in the active anabolic agent/excipient blend being fully entrapped by the ethyl cellulose chains.

25 For the immediate-release formulation, compositions such as the commercially available zeranol product, such as, for example, Ralgro®, may be used and compressed into suitable size tablets. Any optional ingredients such as, for example, dye and the like, may be mixed in before compressing into tablets.

30 The inventive dual formulation is prepared by taking a certain number of thus-prepared tablets containing the controlled-release formulation and a certain number of thus-prepared immediate-release formulation (including Ralgro® which is zeranol plus lactose) tablets in the

injection device. The number of each kind is determined based on the total amount of zeranol one desires to inject into the animal. For comparison purposes, the dual formulation injection may be compared with injection of either the controlled formulation tablets alone or the zeranol tablets alone
5 such that the total amount of zeranol would still match with the total zeranol in the inventive dual formulation. The growth enhancement implant pellets are generally subcutaneously injected into the cattle, or other domesticated animal under the ear. After administration, water diffuses into the tablet from the tissue of the animal and is driven by hydration of the lactose and
10 to a small extent by hydration of the anabolic agent. The dissolved active then diffuses out of the matrix structure and into the animal's systemic circulation. As the EXAMPLES demonstrate, Applicants found that the inventive dual formulation tablets surprisingly resulted in a higher increase of growth and weight gain in the test animals than either the controlled-
15 release tablets alone or the zeranol tablets alone.

Another embodiment of the present invention discloses anabolic implant compositions and formulations for stimulating increased rate of growth, greater amount of growth and greater feed efficiency in cattle. The inventive composition is a dual release formulation which comprises: (i) an
20 immediate-release formulation containing an anabolic agent, and (ii) a controlled-release formulation containing an anabolic agent and a controlled-release agent, wherein the immediate-release formulation and the controlled-release formulation cooperate to effect the desired stimulation of growth and weight gain. The types and examples of (i) and
25 (ii) are described above.

A further embodiment of the present invention discloses a method of stimulating increased rate of growth, greater amount of growth and greater feed efficiency in cattle, whose growth, weight gain and feed efficiency need to be improved, by administering to said cattle an anabolic implant
30 composition which is a dual release formulation which comprises: (i) an immediate-release formulation containing an anabolic agent, and (ii) a controlled-release formulation containing an anabolic agent and a controlled-release agent, wherein the immediate-release formulation and the controlled-release formulation cooperate to effect the desired

stimulation of growth and weight gain. The types and examples of (i) and (ii) are described above.

A still further embodiment of the present invention concerns a method for stimulating increased rate of growth, greater amount of growth and greater feed efficiency in an animal. The method comprises: preparing an immediate-release formulation comprising an anabolic agent such as, for example, the agents described above, in a shaped object suitable for loading into a device such as, for example, pellets, tablets and the like, which device is suitable for administration of said shaped object into the animal (such as, for example, the pistol described earlier); preparing a controlled-release formulation containing an anabolic agent and a controlled-release agent, in a shaped object similar to above and suitable for loading into the device in step (a), wherein said anabolic agent in step (a) and said anabolic agent in step (b) may be the same or different; loading the device with the shapely object in step (a) and the shapely object in step (b) in a ratio such that the total anabolic agent is in the 50-95 weight percent range based on the combined weight of the two formulations (i.e. the formulation in step (a) and the formulation in step (b)); and administering the shaped objects into the animal, wherein said immediate-release formulation and said controlled-release formulation cooperate to effect the desired stimulation. Suitable controlled agents and methods for making the formulations are described above.

The following EXAMPLES are provided to more fully describe how to make and use the implants of the present invention, as well as to demonstrate the superior results attained thereby. It should be noted however that the examples are for illustrative purposes only and that minor changes or variations may be made in the amounts and/or methods that are not covered therein. It should also be noted that to the extent any such changes or variations that do not materially alter the composition or effects of the final product are deemed as falling within the spirit and scope of the present invention as later recited in the claims.

EXAMPLES

EXAMPLE 1: Comparison of Weight Gain with Zeranol as Immediate-release Formulation to a Formulation Containing Zeranol

5 as Controlled-release Formulation: The following zeranol matrix base formulations were prepared to compare controlled-release formulations containing zeranol with Ralgro® and a placebo (an ineffective control). As stated earlier, Ralgro® is a commercially available product of zeranol and lactose.

10

| <u>Formulation</u> | <u>Composition</u> |
|--------------------|--|
| A | Controlled-release Formulation: zeranol/poly(D,L-lactide-co-glycolide copolymer; 50:50 wt%) (180 mg total zeranol) |
| 15 B | Controlled-release Formulation: zeranol/ethyl cellulose (50:50 wt%, 180 mg total zeranol) |
| C | Ralgro® (36 mg zeranol) |
| D | Placebo: no Zeranol |

20

The implants were prepared as follows. For formulation A, the poly (D,L-lactide-co-glycolide 50:50, 3.991 g) was placed in an Erlenmeyer flask and dissolved in 50 grams of ethyl acetate. Separately, the zeranol and lactose (26.606 g) were mixed together dry in a mortar to which the FD & C coloring dyes (0.44 g) were added. The solvent comprising D,L-lactide-co-glycolide and ethyl acetate was then added to the zeranol/dye/lactose mixture. The composition was then heated to 40-45°C. to complete dryness and granulated and sized through a 25 mesh screen. A Cab-O-Sil® silica glidant (0.665 g) was added along with magnesium stearate (1.33 g) which was added as a lubricant. The compositions were then

25

30 compressed in a tableting die to obtain solid implants (26.606 mg each implant) with a hardness of 12-20 Strong Cobb units. Formulation B was prepared in a similar manner using ethyl cellulose as the polymer matrix and Aquacoat ECD-30 instead of ethyl acetate. For formulation C, Ralgro®

was made into similar size tablets using procedures known in the art. And formulation D, the control with no zeranol was made into tablets similar to in formulation C.

The implants were administered to twenty (20) steers subcutaneously under the ear. In order to properly compare the formulations of the present invention with those of the prior art, formulation C was administered twice, once at day 0 and again at day 70, each dose containing 36 mg of zeranol. Each steer was weighed at selected time periods during its development and the average body weight for each group given a particular formulation A to D was calculated for each date and are as follows:

Table 1

| 15 | Treatment | Day | Day | Day | Day | Day | Day | Day | Day | Day |
|----|-----------|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| | | 0 | 28 | 56 | 70 | 84 | 112 | 140 | 168 | 182 |
| 20 | A | 339 | 423 | 483 | 544 | 562 | 616 | 693 | 765 | 803 |
| | B | 337 | 426 | 492 | 558 | 568 | 631 | 701 | 780 | 806 |
| | C | 339 | 431 | 506 | 562 | 578 | 644 | 716 | 812 | 838 |
| | D | 342 | 420 | 473 | 531 | 536 | 593 | 645 | 709 | 742 |

The results show that the weight gain with either controlled-release formulation (A or B) is slightly lower than or, at best, statistically equivalent to that of the Ralgro® re-implant program of formulation C.

Example 2: Comparison of Weight Gain with Inventive Dual Formulation versus Weight Gain with Immediate Formulation alone, or

with Controlled Formulation alone: The effects of implanting the dual immediate-release/controlled-release pellets of the present invention on weight and growth gain were studied and compared with zeranol (as

Ralgro[®]) alone, with controlled-release formulation alone and with a non-effective placebo control. That could be done by replacing certain controlled-release tablets of Example 1 with Ralgro[®] tablet(s). The administered dosages were as follows. The total weight administered is shown in brackets.

Formulation Composition

- | | | |
|----|---|--|
| | E | Placebo control; no zeranol |
| 10 | F | Ralgro [®] (36 mg zeranol; 3 pellets 12 mg each) |
| | G | Zeranol immediate-release (1 pellet of 18 mg zeranol) + Zeranol controlled-release-poly (D,L,-lactide-co-glycoside) (80 mg zeranol; 4 pellets of 20 mg each) [98 mg total zeranol] |
| 15 | H | Zeranol immediate-release (1 pellet of 18 mg zeranol) + Zeranol controlled-release /poly (D,L-lactide-co-glycolide) (160 mg zeranol; 8 pellets of 20 mg zeranol each) [178 mg total zeranol] |
| | I | Zeranol immediate-release (1 pellet of 18 mg zeranol) + Zeranol controlled-release /ethyl cellulose (160 mg zeranol; 8 pellets of 20 mg zeranol each) [178 mg total zeranol] |
| 20 | J | Zeranol immediate-release (1 pellet of 18 mg zeranol) + Zeranol controlled-release /ethyl cellulose (80 mg zeranol; 4 pellets of 20 mg zeranol each) [98 mg zeranol total] |

As can be seen, to prepare the inventive dual formulations H and I, one zeranol immediate-release pellet and 8 zeranol controlled-release pellets were taken in the device. Similarly, to prepare the inventive dual formulations G and J containing just half the amount of the controlled-release formulation, one zeranol immediate-release pellet and 4 controlled-release pellets were taken in the device. The immediate-release pellets and control release pellets were formulated as in Example 1 and administered to six groups of cattle in a similar fashion, i.e., subcutaneously under the ear. Again, in order to compare the improved formulations with the prescriptions currently followed in the veterinary art,

formulation F was administered twice, once (36 mg) at day 0 and again (36 mg) at day 70. Each steer was weighed at different intervals during its development and the average weight for each group given a particular formulation was averaged for each date. The formulations and average weight gain results for each are as follows:

Table 2

| Treatment Formulation | <u>Average Body Weight (in kilograms)</u> | | | | | | |
|-----------------------|---|-------|--------|--------|--------|---------|---------|
| | Day (-1) | Day 0 | Day 28 | Day 56 | Day 84 | Day 112 | Day 140 |
| E | 309 | 303 | 352 | 389 | 425 | 461 | 491 |
| F | 309 | 300 | 356 | 398 | 435 | 477 | 511 |
| G | 308 | 301 | 354 | 401 | 444 | 485 | 525 |
| H | 309 | 302 | 358 | 404 | 445 | 485 | 525 |
| I | 309 | 302 | 357 | 408 | 451 | 494 | 533 |
| J | 309 | 302 | 356 | 402 | 443 | 481 | 518 |

As is evidenced by the results shown for formulations G-J, superior growth and weight gains were observed with the inventive dual release formulations. Thus, when one (out of nine) of the controlled-release formulation pellets was replaced with one immediate-release pellet (formulations H and I), the weight gain became significantly higher than the results observed following the standard immediate re-implant program (formulation F) above. Such improvement was also noticed even when the controlled-release fraction was reduced by half (from 160 to 80 mg or 8 to 4 pellets) as shown in formulations G and J.

CLAIMS

What is claimed is:

1. An anabolic implant composition for stimulating increased rate of growth, greater amount of growth and greater feed efficiency in cattle, said composition comprising: (i) an immediate-release formulation comprising an anabolic agent, and (ii) a controlled-release formulation comprising an anabolic agent and a controlled-release agent, wherein said immediate-release formulation and said controlled-release formulation cooperate to effect said stimulation.
2. The implant composition of claim 1, wherein said immediate-release formulation and said controlled-release formulation are present respectively in a weight ratio range 1:2 to 1:25 in said composition.
3. The implant composition of claim 1, wherein said immediate-release formulation and said controlled-release formulation are present respectively in a weight ratio range 1:2 to 1:10 in said composition.
4. The implant composition of claim 1, wherein said immediate-release formulation and said controlled-release formulation are present respectively in a weight ratio range 1:3 to 1:8 in said composition.
5. The implant composition of claim 1, wherein said composition is subcutaneously injectable in said cattle.
6. The implant composition of claim 1, wherein said immediate-release formulation and said controlled-release formulation contain the same anabolic agent.
7. The implant composition of claim 1, wherein said immediate-release formulation and said controlled-release formulation contain different anabolic agents.
8. The implant composition of claim 1, wherein said anabolic agent is selected from the group consisting of zeranol, estradiol, estradiol benzoate, trenbolone, trenbolone acetate, somatotrophin, testosterone, testosterone propionate, salbutamol, progesterone, and combinations, salts and derivatives thereof.
9. The implant composition of claim 8, wherein said anabolic agent is zeranol.

10. The implant composition of claim 8, wherein said anabolic agent is trenbolone acetate.

11. The implant composition of claim 9, wherein said zeranol is the anabolic agent in both said immediate-release formulation and said
5 controlled-release formulation and comprises from about 50 wt.% to about 95 wt.% of said composition based on a total weight percentage basis.

12. The implant composition of claim 9, wherein said zeranol is the anabolic agent in both said immediate-release formulation and said
10 controlled-release formulation and comprises from about 60 wt.% to about 80 wt % of said composition.

13. The implant composition of claim 1, wherein said immediate-release formulation additionally contains a diluent.

14. The implant composition of claim 13, wherein said diluent is selected from the group consisting of lactose, mannitol, sorbitol, sucrose,
15 dextrose, starches, hydrolyzed starches, and combinations thereof.

15. The implant composition of claim 14, wherein said diluent is lactose.

16. The implant composition of claim 1, wherein said controlled-release agent is selected from the group consisting of poly(D,L-lactide-co-glycolide), ethyl cellulose, methyl acrylate-methyl methacrylate copolymer,
20 methyl cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, sodium carboxymethyl cellulose, and combinations thereof.

17. The implant composition of claim 16, wherein said controlled-release agent is poly(D,L-lactide-co-glycolide).

18. The implant composition of claim 16, wherein said controlled-release
25 agent is ethyl cellulose.

19. The implant composition of claim 1, wherein said controlled-release agent comprises from about 1.0 wt.% to about 8.0 wt.% based on the total weight of said implant composition.

20. The implant composition of claim 1, further comprising a bulking
30 agent, binder, excipient, tableting agent, colorant and combinations thereof.

21. A method for stimulating increased rate of growth, greater amount of
growth and greater feed efficiency in cattle, comprising the administration
of an anabolic implant composition to said cattle which composition

comprises: (i) an immediate-release formulation comprising an anabolic agent, and (ii) a controlled-release formulation comprising an anabolic agent and a controlled-release agent, wherein said immediate-release formulation and said controlled-release formulation cooperate to effect said stimulation.

22. The method of claim 21, wherein said immediate-release formulation and said controlled-release formulation are present in a weight ratio 1:25 in said composition.

23. The method of claim 21, wherein said administration comprises subcutaneously injecting said composition into said cattle.

24. The method of claim 21, wherein said immediate-release formulation and said controlled-release formulation contain the same anabolic agent.

25. The method of claim 21, wherein said immediate-release formulation and said controlled-release formulation contain different anabolic agents.

26. The method of claim 21, wherein said anabolic agent is selected from the group consisting of zeranol, estradiol, estradiol benzoate, trenbolone, trenbolone acetate, somatotrophin, testosterone, testosterone propionate, salbutamol, progesterone, and combinations, salts and derivatives thereof.

27. The method of claim 26, wherein said anabolic agent is zeranol.

28. The method of claim 27, wherein said zeranol is the anabolic agent in both said immediate-release formulation and said controlled-release formulation and comprises from about 50 wt.% to about 95 wt.% of said composition.

29. The method of claim 27, wherein zeranol is the anabolic agent in both said immediate-release formulation and said controlled-release formulation and comprises from about 60 wt.% to about 80 wt % of said composition.

30. The method of claim 21, wherein said immediate-release formulation additionally contains a diluent.

31. The method of claim 30, wherein said diluent is selected from the group consisting of lactose, mannitol, sorbitol, sucrose, dextrose, starches, hydrolyzed starches, and combinations thereof.

32. The method of claim 31, wherein said diluent is lactose.

5 33. The method of claim 21, wherein said controlled-release agent is selected from the group consisting of poly(D,L-lactide-co-glycolide), ethyl cellulose, methyl acrylate-methyl methacrylate copolymer, methyl cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, sodium carboxymethyl cellulose, and combinations thereof.

10 34. The method of claim 33, wherein said controlled-release agent is poly(D,L-lactide-co-glycolide).

35. The method of claim 33, wherein said controlled-release agent is ethyl cellulose.

15 36. The method of claim 21, further comprising a bulking agent, binder, tableting agent, excipient, colorant and combinations thereof.

37. A method for stimulating increased rate of growth, greater amount of growth and greater feed efficiency in an animal, said process comprising:

(a) preparing an immediate-release formulation comprising an anabolic agent, in a first shaped object suitable for loading into a device which device is suitable for administration of said shaped object into the animal;

20 (b) preparing a controlled-release formulation comprising an anabolic agent and a controlled-release agent, in a second shaped object suitable for loading into said device in step (a), wherein said anabolic agent in step (a) and said anabolic agent in step (b) may be the same or different,

25 (c) loading said device with said first shaped object and said second shaped object in a ratio such that the total anabolic agent is in the 50-95 weight percent range based on the combined weight of said formulation in step (a) and said formulation in step (b); and

30 (d) administering said shaped objects into the animal, wherein said immediate-release formulation and said controlled-release formulation cooperate to effect the stimulation.

38. The method of claim 37, wherein said anabolic agent in step 9a) and step (b) is the same and is zeranol.

39. The method of claim 37, wherein said controlled-release agent in step (b) is poly(D,L-lactide-co-glycolide), ethyl cellulose, methyl acrylate-methyl methacrylate copolymer, methyl cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, sodium carboxymethyl cellulose, and combinations thereof.
40. The method of claim 37, further containing lactose in step (a), step (b) or both.
41. The method of claim 37, wherein said first shaped object, or said second shaped object, or both is a tablet.
42. The method of claim 37, wherein said first shaped object, said second shaped object, or both is a pellet.

ABSTRACT OF THE INVENTION

An improved weight and growth stimulant for domesticated animals such as cattle, pigs and sheep is comprised of an anabolic agent that is subcutaneously administered in the form of a dual release implant
5 formulation. Increased gains are particularly improved when zeranol is administered in an immediate-release and controlled-release formulation which allows for a one-time dosage injection.

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**DECLARATION FOR UTILITY OR
DESIGN
PATENT APPLICATION
(37 CFR 1.63)**

☒ Declaration Submitted with Initial Filing **OR** ☐ Declaration Submitted after Initial Filing (surcharge (37 CFR 1.16 (e)) required)

Attorney Docket Number AH0948Q

First Named Inventor SHIH, et al

COMPLETE IF KNOWN

Application Number /

Filing Date November 2, 1999

Group Art Unit TO BE ADVISED

Examiner Name TO BE ADVISED

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

IMPROVED GROWTH STIMULANT COMPOSITIONS

the specification of which (Title of the Invention)

☒ is attached hereto
OR

☐ was filed on (MM/DD/YYYY) as United States Application Number or PCT International

Application Number and was amended on (MM/DD/YYYY) (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

| Prior Foreign Application Number(s) | Country | Foreign Filing Date (MM/DD/YYYY) | Priority Not Claimed | Certified Copy Attached? | |
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| U.S. Parent Application or PCT Parent Number | Parent Filing Date (MM/DD/YYYY) | Parent Patent Number (if applicable) |
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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor: ☐ A petition has been filed for this unsigned inventor

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☒ Additional inventors are being named on the 2 supplemental Additional Inventor(s) sheet(s) PTO/SB/02A attached hereto

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| Edwin P. Ching | 34090 | Susan Lee | 30653 |
| Eric S. Dicker | 31669 | Anita W. Magatti | 29825 |
| Cynthia L. Foulke | 32364 | Arthur Mann | 35598 |
| Robert A. Franks | 28605 | Edward H. Mazer | 27573 |
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| James M. Gould | 33702 | Richard B. Murphy | 35296 |
| Richard J. Grochala | 31518 | James R. Nelson | 27929 |
| Henry S. Hadad | 35888 | David B. Schram | 43096 |
| Thomas D. Hoffman | 28221 | Immac J. Thampoe | 36322 |
| Henry C. Jeanette | 30856 | Paul A. Thompson | 35385 |
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| | First Named Inventor | SHIH, et al |
| | COMPLETE IF KNOWN | |
| | Application Number | / |
| | Filing Date | November 2, 1999 |
| | Group Art Unit | TO BE ADVISED |
| | Examiner Name | TO BE ADVISED |

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

IMPROVED GROWTH STIMULANT COMPOSITIONS

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OR
☐ was filed on (MM/DD/YYYY) [] as United States Application Number or PCT International Application Number [] and was amended on (MM/DD/YYYY) [] (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

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| | | |

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As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

☐ Customer Number

OR

☒ Registered practitioner(s) name/registration number listed below

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| Name | Registration Number | Name | Registration Number |
|------|---------------------|------|---------------------|
| | | | |

☒ Additional registered practitioner(s) named on supplemental Registered Practitioner Information sheet PTO/SB/02C attached hereto.

Direct all correspondence to: ☐ Customer Number or Bar Code Label

OR ☒ Correspondence address below

| | | | | | |
|---------|--|-----------|----------------|-----|----------------|
| Name | PALAIYUR S. KALYANARAMAN | | | | |
| Address | Patent Dept. K-6-1, 1990 Schering-Plough Corporation | | | | |
| Address | 2000 Galloping Hill Road | | | | |
| City | Kenilworth | State | NJ | ZIP | 07033-0530 |
| Country | USA | Telephone | (908) 298-5037 | Fax | (908) 298-5388 |

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

| | | | | | |
|--|------------------------|---|------------------------|---------|--------|
| Name of Sole or First Inventor: | | <input type="checkbox"/> A petition has been filed for this unsigned inventor | | | |
| Given Name (first and middle (if any)) | | | Family Name or Surname | | |
| CHUNG | | | SHIH | | |
| Inventor's Signature | | | | | Date |
| Residence: City | Sandy | State | UT | Country | U.S.A. |
| Post Office Address | 2798 E. Amberwick Lane | | | | |
| Post Office Address | | | | | |
| City | Sandy | State | UT | ZIP | 84093 |
| | | | | Country | U.S.A. |

☒ Additional inventors are being named on the 2 supplemental Additional Inventor(s) sheet(s) PTO/SB/02A attached hereto

Please type a plus sign (+) inside this box → ☐

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DECLARATION

ADDITIONAL INVENTOR(S)
Supplemental Sheet
Page 1 of 2

| | | | | | | | |
|---|---------------|----------------------------|----|---|------------|-------------|--------|
| Name of Additional Joint Inventor, if any: | | | | <input type="checkbox"/> A petition has been filed for this unsigned inventor | | | |
| Given Name (first and middle [if any]) | | | | Family Name or Surname | | | |
| THOMAS J. | | | | KENNEDY | | | |
| Inventor's Signature | | | | Date | | | |
| Residence: City | WAUNAKEE | State | WI | Country | U.S.A. | Citizenship | U.S.A. |
| Post Office Address | | 5492 Kennedy Drive | | | | | |
| Post Office Address | | | | | | | |
| City | Waunakee | State | WI | ZIP | 53597 | Country | U.S.A. |
| Name of Additional Joint Inventor, if any: | | | | <input type="checkbox"/> A petition has been filed for this unsigned inventor | | | |
| Given Name (first and middle [if any]) | | | | Family Name or Surname | | | |
| PETER JAMES | | | | KNIGHT | | | |
| Inventor's Signature | | | | Date | | | |
| Residence: City | Stewartsville | State | NJ | Country | U.S.A.. | Citizenship | UK |
| Post Office Address | | 1826 Gary Road | | | | | |
| Post Office Address | | | | | | | |
| City | Warren | State | NJ | ZIP | 08886 | Country | U.S.A. |
| Name of Additional Joint Inventor, if any: | | | | <input type="checkbox"/> A petition has been filed for this unsigned inventor | | | |
| Given Name (first and middle [if any]) | | | | Family Name or Surname | | | |
| DANIEL S. | | | | ROBINS | | | |
| Inventor's Signature | | | | Date | | | |
| Residence: City | New York | State | NY | Country | U.S.A. | Citizenship | U.S.A. |
| Post Office Address | | 77 E. 12th Street, Apt. 3B | | | | | |
| Post Office Address | | | | | | | |
| City | New York | State | NY | ZIP | 10003-5003 | Country | U.S.A. |

Burden Hour Statement: This form is estimated to take 0.4 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231.

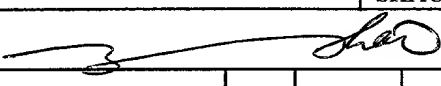
Please type a plus sign (+) inside this box → ☐

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ADDITIONAL INVENTOR(S)
Supplemental Sheet
Page 2 of 2

| | | | | | | | |
|---|--|---|--|---|--|----------|--|
| Name of Additional Joint Inventor, if any: | | | | <input type="checkbox"/> A petition has been filed for this unsigned inventor | | | |
| Given Name (first and middle [if any]) | | | | Family Name or Surname | | | |
| ZEZHI, JESSE | | | | SHAO | | | |
| Inventor's Signature | |  | | Date | | 10/18/99 | |
| Residence: City | | BASKING RIDGE | | State | | NJ | |
| | | | | Country | | U.S.A. | |
| Post Office Address | | 68 Patriot Hill Drive | | | | | |
| Post Office Address | | | | | | | |
| City | | Basking Ridge | | State | | NJ | |
| | | | | ZIP | | 07920 | |
| | | | | Country | | U.S.A. | |
| Name of Additional Joint Inventor, if any: | | | | <input type="checkbox"/> A petition has been filed for this unsigned inventor | | | |
| Given Name (first and middle [if any]) | | | | Family Name or Surname | | | |
| | | | | | | | |
| Inventor's Signature | | | | Date | | | |
| Residence: City | | | | State | | | |
| | | | | Country | | | |
| Post Office Address | | | | | | | |
| Post Office Address | | | | | | | |
| City | | | | State | | | |
| | | | | ZIP | | | |
| | | | | Country | | | |
| Name of Additional Joint Inventor, if any: | | | | <input type="checkbox"/> A petition has been filed for this unsigned inventor | | | |
| Given Name (first and middle [if any]) | | | | Family Name or Surname | | | |
| | | | | | | | |
| Inventor's Signature | | | | Date | | | |
| Residence: City | | | | State | | | |
| | | | | Country | | | |
| Post Office Address | | | | | | | |
| Post Office Address | | | | | | | |
| City | | | | State | | | |
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DECLARATION

REGISTERED PRACTITIONER INFORMATION (Supplemental Sheet)

| Name | Registration Number | Name | Registration Number |
|--------------------------|------------------------|--------------------|------------------------|
| Carl W. Battle | 30731 | Gabriel P. Kralik | 34855 |
| Edwin P. Ching | 34090 | Susan Lee | 30653 |
| Eric S. Dicker | 31669 | Anita W. Magatti | 29825 |
| Cynthia L. Foulke | 32364 | Arthur Mann | 35598 |
| Robert A. Franks | 28605 | Edward H. Mazer | 27573 |
| Kenneth M. Goldman | 34174 | Jaye P. McLaughlin | 41211 |
| James M. Gould | 33702 | Richard B. Murphy | 35296 |
| Richard J. Grochala | 31518 | James R. Nelson | 27929 |
| Henry S. Hadad | 35888 | David B. Schram | 43096 |
| Thomas D. Hoffman | 28221 | Immac J. Thampoe | 36322 |
| Henry C. Jeanette | 30856 | Paul A. Thompson | 35385 |
| Palaiyur S. Kalyanaraman | 34634 | Joanne P. Will | 35737 |
| Gerald P. Keleher | 43707 | Donald W. Wyatt | 40879 |

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| | | |
|---|-------------------------------|------------------|
| DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63) <input checked="" type="checkbox"/> Declaration Submitted with Initial Filing OR <input type="checkbox"/> Declaration Submitted after Initial Filing (surcharge (37 CFR 1.16 (e)) required) | Attorney Docket Number | AH0948Q |
| | First Named Inventor | SHIH, et al |
| | COMPLETE IF KNOWN | |
| | Application Number | / |
| | Filing Date | November 2, 1999 |
| | Group Art Unit | TO BE ADVISED |
| | Examiner Name | TO BE ADVISED |

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

IMPROVED GROWTH STIMULANT COMPOSITIONS

the specification of which (Title of the Invention)
☒ is attached hereto
OR
☐ was filed on (MM/DD/YYYY) _____ as United States Application Number or PCT International Application Number _____ and was amended on (MM/DD/YYYY) _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT International application having a filing date before that of the application on which priority is claimed.

| Prior Foreign Application Number(s) | Country | Foreign Filing Date (MM/DD/YYYY) | Priority Not Claimed | Certified Copy Attached? | |
|-------------------------------------|---------|----------------------------------|--------------------------|--------------------------|--------------------------|
| | | | | YES | NO |
| | | | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| | | | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| | | | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| | | | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto:

I hereby claim the benefit under 35 U.S.C. 119(e) of any United States provisional application(s) listed below.

| Application Number(s) | Filing Date (MM/DD/YYYY) |
|-----------------------|--------------------------|
| 60/107,056 | 11/04/98 |

☐ Additional provisional application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

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| | | |
|--|--|------|
| CERTIFICATE OF MAILING | | |
| I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231 on this date: _____ | | |
| Typed or printed name | | |
| Signature | | Date |

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| Express Mail Label No. | EL226882657US |
| Date | Nov. 2, 1999 |

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DECLARATION — Utility or Design Patent Application

I hereby claim the benefit under 35 U.S.C. 120 of any United States application(s), or 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

| U.S. Parent Application or PCT Parent Number | Parent Filing Date (MM/DD/YYYY) | Parent Patent Number (if applicable) |
|--|---------------------------------|--------------------------------------|
| | | |

☐ Additional U.S. or PCT international application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

☐ Customer Number OR ☒ Registered practitioner(s) name/registration number listed below

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| | | | |

☒ Additional registered practitioner(s) named on supplemental Registered Practitioner Information sheet PTO/SB/02C attached hereto.

Direct all correspondence to: ☐ Customer Number OR ☒ Correspondence address below

| | | | | | |
|---------|--|-----------|----------------|-----|----------------|
| Name | PALAIYUR S. KALYANARAMAN | | | | |
| Address | Patent Dept. K-6-1, 1990 Schering-Plough Corporation | | | | |
| Address | 2000 Galloping Hill Road | | | | |
| City | Kenilworth | State | NJ | ZIP | 07033-0530 |
| Country | USA | Telephone | (908) 298-5037 | Fax | (908) 298-5388 |

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor: ☐ A petition has been filed for this unsigned inventor

| | |
|--|------------------------|
| Given Name (first and middle (if any)) | Family Name or Surname |
| CHUNG | SHIH |

| | | | | | | | |
|----------------------|------------------|-------|----------|---------|--------|-------------|--------|
| Inventor's Signature | <i>Chun Shih</i> | Date | 04/19/99 | | | | |
| Residence: City | Sandy | State | UT | Country | U.S.A. | Citizenship | U.S.A. |

| | | | |
|---------------------|------------------------|--|--|
| Post Office Address | 2798 E. Amberwick Lane | | |
| Post Office Address | | | |

| | | | | | | | |
|------|-------|-------|----|-----|-------|---------|--------|
| City | Sandy | State | UT | ZIP | 84093 | Country | U.S.A. |
|------|-------|-------|----|-----|-------|---------|--------|

☒ Additional inventors are being named on the 2 supplemental Additional Inventor(s) sheet(s) PTO/SB/02A attached hereto

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Supplemental Sheet
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| | | | | | | | |
|---|---------------|----------------------------|----|---|------------|-------------|--------|
| Name of Additional Joint Inventor, if any: | | | | <input type="checkbox"/> A petition has been filed for this unsigned inventor | | | |
| Given Name (first and middle [if any]) | | | | Family Name or Surname | | | |
| THOMAS J. | | | | KENNEDY | | | |
| Inventor's Signature | | | | Date | | | |
| Residence: City | WAUNAKEE | State | WI | Country | U.S.A. | Citizenship | U.S.A. |
| Post Office Address | | 5492 Kennedy Drive | | | | | |
| Post Office Address | | | | | | | |
| City | Waunakee | State | WI | ZIP | 53597 | Country | U.S.A. |
| Name of Additional Joint Inventor, if any: | | | | <input type="checkbox"/> A petition has been filed for this unsigned inventor | | | |
| Given Name (first and middle [if any]) | | | | Family Name or Surname | | | |
| PETER JAMES | | | | KNIGHT | | | |
| Inventor's Signature | | | | Date | | | |
| Residence: City | Stewartsville | State | NJ | Country | U.S.A.. | Citizenship | UK |
| Post Office Address | | 1826 Gary Road | | | | | |
| Post Office Address | | | | | | | |
| City | Warren | State | NJ | ZIP | 08886 | Country | U.S.A. |
| Name of Additional Joint Inventor, if any: | | | | <input type="checkbox"/> A petition has been filed for this unsigned inventor | | | |
| Given Name (first and middle [if any]) | | | | Family Name or Surname | | | |
| DANIEL S. | | | | ROBINS | | | |
| Inventor's Signature | | | | Date | | | |
| Residence: City | New York | State | NY | Country | U.S.A. | Citizenship | U.S.A. |
| Post Office Address | | 77 E. 12th Street, Apt. 3B | | | | | |
| Post Office Address | | | | | | | |
| City | New York | State | NY | ZIP | 10003-5003 | Country | U.S.A. |

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ADDITIONAL INVENTOR(S)
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Page 2 of 2

| | | | | | | | | |
|---|--|-----------------------|-------|------------------------|---|--------|-------------|--------|
| Name of Additional Joint Inventor, if any: | | | | | <input type="checkbox"/> A petition has been filed for this unsigned inventor | | | |
| Given Name (first and middle [if any]) | | | | Family Name or Surname | | | | |
| ZEZHI, JESSE | | | | SHAO | | | | |
| Inventor's Signature | | | | | Date | | | |
| Residence: City | | BASKING RIDGE | State | NJ | Country | U.S.A. | Citizenship | U.S.A. |
| Post Office Address | | 68 Patriot Hill Drive | | | | | | |
| Post Office Address | | | | | | | | |
| City | | Basking Ridge | State | NJ | ZIP | 07920 | Country | U.S.A. |
| Name of Additional Joint Inventor, if any: | | | | | <input type="checkbox"/> A petition has been filed for this unsigned inventor | | | |
| Given Name (first and middle [if any]) | | | | Family Name or Surname | | | | |
| | | | | | | | | |
| Inventor's Signature | | | | | Date | | | |
| Residence: City | | | State | | Country | | Citizenship | |
| Post Office Address | | | | | | | | |
| Post Office Address | | | | | | | | |
| City | | | State | | ZIP | | Country | |
| Name of Additional Joint Inventor, if any: | | | | | <input type="checkbox"/> A petition has been filed for this unsigned inventor | | | |
| Given Name (first and middle [if any]) | | | | Family Name or Surname | | | | |
| | | | | | | | | |
| Inventor's Signature | | | | | Date | | | |
| Residence: City | | | State | | Country | | Citizenship | |
| Post Office Address | | | | | | | | |
| Post Office Address | | | | | | | | |
| City | | | State | | ZIP | | Country | |

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DECLARATION

REGISTERED PRACTITIONER INFORMATION (Supplemental Sheet)

| Name | Registration Number | Name | Registration Number |
|--------------------------|------------------------|--------------------|------------------------|
| Carl W. Battle | 30731 | Gabriel P. Kralik | 34855 |
| Edwin P. Ching | 34090 | Susan Lee | 30653 |
| Eric S. Dicker | 31669 | Anita W. Magatti | 29825 |
| Cynthia L. Foulke | 32364 | Arthur Mann | 35598 |
| Robert A. Franks | 28605 | Edward H. Mazer | 27573 |
| Kenneth M. Goldman | 34174 | Jaye P. McLaughlin | 41211 |
| James M. Gould | 33702 | Richard B. Murphy | 35296 |
| Richard J. Grochala | 31518 | James R. Nelson | 27929 |
| Henry S. Hadad | 35888 | David B. Schram | 43096 |
| Thomas D. Hoffman | 28221 | Immac J. Thampoe | 36322 |
| Henry C. Jeanette | 30856 | Paul A. Thompson | 35385 |
| Palaiyur S. Kalyanaraman | 34634 | Joanne P. Will | 35737 |
| Gerald P. Keleher | 43707 | Donald W. Wyatt | 40879 |

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| | | |
|--|-------------------------------|------------------|
| DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63) <input type="checkbox"/> Declaration Submitted with Initial Filing <input type="checkbox"/> Declaration Submitted after Initial Filing (surcharge (37 CFR 1.16 (e)) required) | Attorney Docket Number | AH0948Q |
| | First Named Inventor | SHIH, et al |
| | COMPLETE IF KNOWN | |
| | Application Number | / |
| | Filing Date | November 3, 1999 |
| | Group Art Unit | TO BE ADVISED |
| | Examiner Name | TO BE ADVISED |

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

IMPROVED GROWTH STIMULANT COMPOSITIONS

the specification of which ☒ is attached hereto (Title of the Invention)

OR
☐ was filed on (MM/DD/YYYY) as United States Application Number or PCT International

Application Number and was amended on (MM/DD/YYYY) (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

| Prior Foreign Application Number(s) | Country | Foreign Filing Date (MM/DD/YYYY) | Priority Not Claimed | Certified Copy Attached? | |
|-------------------------------------|---------|----------------------------------|--------------------------|--------------------------|--------------------------|
| | | | | YES | NO |
| | | | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| | | | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| | | | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| | | | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto:

I hereby claim the benefit under 35 U.S.C. 119(e) of any United States provisional application(s) listed below.

| Application Number(s) | Filing Date (MM/DD/YYYY) | <input type="checkbox"/> Additional provisional application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto. |
|-----------------------|--------------------------|--|
| 60/107,056 | 11/04/98 | |

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CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231 on this date:

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Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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DECLARATION — Utility or Design Patent Application

I hereby claim the benefit under 35 U.S.C. 120 of any United States application(s), or 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

| U.S. Parent Application or PCT Parent Number | Parent Filing Date (MM/DD/YYYY) | Parent Patent Number (if applicable) |
|--|---------------------------------|--------------------------------------|
| | | |

☐ Additional U.S. or PCT international application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

☐ Customer Number

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☒ Registered practitioner(s) name/registration number listed below

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| | | | |

☒ Additional registered practitioner(s) named on supplemental Registered Practitioner Information sheet PTO/SB/02C attached hereto.

Direct all correspondence to: ☐ Customer Number or Bar Code Label OR ☒ Correspondence address below

| | | | | | |
|---------|--|-----------|----------------|-----|----------------|
| Name | PALAIYUR S. KALYANARAMAN | | | | |
| Address | Patent Dept. K-6-1, 1990 Schering-Plough Corporation | | | | |
| Address | 2000 Galloping Hill Road | | | | |
| City | Kenilworth | State | NJ | ZIP | 07033-0530 |
| Country | USA | Telephone | (908) 298-5037 | Fax | (908) 298-5388 |

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor: ☐ A petition has been filed for this unsigned inventor

| | | | | | | | |
|--|------------------------|-------|----|------------------------|--------|-------------|--------|
| Given Name (first and middle [if any]) | | | | Family Name or Surname | | | |
| CHUNG | | | | SHIH | | | |
| Inventor's Signature | | | | | | Date | |
| Residence: City | Sandy | State | UT | Country | U.S.A. | Citizenship | U.S.A. |
| Post Office Address | 2798 E. Amberwick Lane | | | | | | |
| Post Office Address | | | | | | | |
| City | Sandy | State | UT | ZIP | 84093 | Country | U.S.A. |

☒ Additional inventors are being named on the 2 supplemental Additional Inventor(s) sheet(s) PTO/SB/02A attached hereto

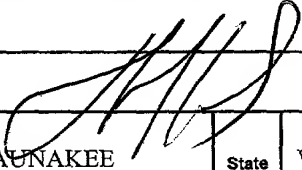
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DECLARATION

ADDITIONAL INVENTOR(S)
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| | | | | | | | |
|--|--|---|--|---|--|------------|--|
| Name of Additional Joint Inventor, if any: | | | | <input type="checkbox"/> A petition has been filed for this unsigned inventor | | | |
| Given Name (first and middle (if any)) | | | | Family Name or Surname | | | |
| THOMAS J. | | | | KENNEDY | | | |
| Inventor's Signature | |  | | Date | | 2/20/99 | |
| Residence: City | | WAUNAKEE | | State | | WI | |
| | | | | Country | | U.S.A. | |
| Post Office Address | | 5492 Kennedy Drive | | | | | |
| Post Office Address | | | | | | | |
| City | | Waunakee | | State | | WI | |
| | | | | ZIP | | 53597 | |
| | | | | Country | | U.S.A. | |
| Name of Additional Joint Inventor, if any: | | | | <input type="checkbox"/> A petition has been filed for this unsigned inventor | | | |
| Given Name (first and middle (if any)) | | | | Family Name or Surname | | | |
| PETER JAMES | | | | KNIGHT | | | |
| Inventor's Signature | | | | Date | | | |
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| | | | | Country | | U.S.A.. | |
| Post Office Address | | 1826 Gary Road | | | | | |
| Post Office Address | | | | | | | |
| City | | Warren | | State | | NJ | |
| | | | | ZIP | | 08886 | |
| | | | | Country | | U.S.A. | |
| Name of Additional Joint Inventor, if any: | | | | <input type="checkbox"/> A petition has been filed for this unsigned inventor | | | |
| Given Name (first and middle (if any)) | | | | Family Name or Surname | | | |
| DANIEL S. | | | | ROBINS | | | |
| Inventor's Signature | | | | Date | | | |
| Residence: City | | New York | | State | | NY | |
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| Post Office Address | | 77 E. 12th Street, Apt. 3B | | | | | |
| Post Office Address | | | | | | | |
| City | | New York | | State | | NY | |
| | | | | ZIP | | 10003-5003 | |
| | | | | Country | | U.S.A. | |

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Supplemental Sheet
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| | | | | | | | |
|---|--|-----------------------|--|---|--|--------|--|
| Name of Additional Joint Inventor, if any: | | | | <input type="checkbox"/> A petition has been filed for this unsigned inventor | | | |
| Given Name (first and middle [if any]) | | | | Family Name or Surname | | | |
| ZEZHI, JESSE | | | | SHAO | | | |
| Inventor's Signature | | | | Date | | | |
| Residence: City | | BASKING RIDGE | | State | | NJ | |
| | | | | Country | | U.S.A. | |
| Post Office Address | | 68 Patriot Hill Drive | | | | | |
| Post Office Address | | | | | | | |
| City | | Basking Ridge | | State | | NJ | |
| | | | | ZIP | | 07920 | |
| | | | | Country | | U.S.A. | |
| Name of Additional Joint Inventor, if any: | | | | <input type="checkbox"/> A petition has been filed for this unsigned inventor | | | |
| Given Name (first and middle [if any]) | | | | Family Name or Surname | | | |
| | | | | | | | |
| Inventor's Signature | | | | Date | | | |
| Residence: City | | | | State | | | |
| | | | | Country | | | |
| Post Office Address | | | | | | | |
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| | | | | ZIP | | | |
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| Given Name (first and middle [if any]) | | | | Family Name or Surname | | | |
| | | | | | | | |
| Inventor's Signature | | | | Date | | | |
| Residence: City | | | | State | | | |
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| Name | Registration Number | Name | Registration Number |
|--------------------------|---------------------|--------------------|---------------------|
| Carl W. Battle | 30731 | Gabriel P. Kralik | 34855 |
| Edwin P. Ching | 34090 | Susan Lee | 30653 |
| Eric S. Dicker | 31669 | Anita W. Magatti | 29825 |
| Cynthia L. Foulke | 32364 | Arthur Mann | 35598 |
| Robert A. Franks | 28605 | Edward H. Mazer | 27573 |
| Kenneth M. Goldman | 34174 | Jaye P. McLaughlin | 41211 |
| James M. Gould | 33702 | Richard B. Murphy | 35296 |
| Richard J. Grochala | 31518 | James R. Nelson | 27929 |
| Henry S. Hadad | 35888 | David B. Schram | 43096 |
| Thomas D. Hoffman | 28221 | Immac J. Thampoe | 36322 |
| Henry C. Jeanette | 30856 | Paul A. Thompson | 35385 |
| Palaiyur S. Kalyanaraman | 34634 | Joanne P. Will | 35737 |
| Gerald P. Keleher | 43707 | Donald W. Wyatt | 40879 |

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| | | |
|---|-------------------------------|------------------|
| DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63) <input checked="" type="checkbox"/> Declaration Submitted with Initial Filing OR <input type="checkbox"/> Declaration Submitted after Initial Filing (surcharge (37 CFR 1.16 (e)) required) | Attorney Docket Number | AH0948Q |
| | First Named Inventor | SHIH, et al |
| | COMPLETE IF KNOWN | |
| | Application Number | / |
| | Filing Date | November 2, 1999 |
| | Group Art Unit | TO BE ADVISED |
| | Examiner Name | TO BE ADVISED |

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

IMPROVED GROWTH STIMULANT COMPOSITIONS

the specification of which
☒ is attached hereto
OR
☐ was filed on (MM/DD/YYYY) [] as United States Application Number or PCT International Application Number [] and was amended on (MM/DD/YYYY) [] (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT International application having a filing date before that of the application on which priority is claimed.

| Prior Foreign Application Number(s) | Country | Foreign Filing Date (MM/DD/YYYY) | Priority Not Claimed | Certified Copy Attached? | |
|-------------------------------------|---------|----------------------------------|--------------------------|--------------------------|--------------------------|
| | | | | YES | NO |
| | | | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| | | | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| | | | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| | | | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto:

I hereby claim the benefit under 35 U.S.C. 119(e) of any United States provisional application(s) listed below.

| Application Number(s) | Filing Date (MM/DD/YYYY) |
|-----------------------|--------------------------|
| 60/107,056 | 11/04/98 |

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| U.S. Parent Application or PCT Parent Number | Parent Filing Date (MM/DD/YYYY) | Parent Patent Number (if applicable) |
|--|---------------------------------|--------------------------------------|
| | | |

☐ Additional U.S. or PCT international application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

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OR ☒ Correspondence address below

| | | | | | |
|---------|--|-----------|----------------|-----|----------------|
| Name | PALAIYUR S. KALYANARAMAN | | | | |
| Address | Patent Dept. K-6-1, 1990 Schering-Plough Corporation | | | | |
| Address | 2000 Galloping Hill Road | | | | |
| City | Kenilworth | State | NJ | ZIP | 07033-0530 |
| Country | USA | Telephone | (908) 298-5037 | Fax | (908) 298-5388 |

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor:

☐ A petition has been filed for this unsigned inventor

| | | | | | | | |
|--|------------------------|------------------------|------|---------|--------|-------------|--------|
| Given Name (first and middle [if any]) | | Family Name or Surname | | | | | |
| CHUNG | | SHIH | | | | | |
| Inventor's Signature | | | Date | | | | |
| Residence: City | Sandy | State | UT | Country | U.S.A. | Citizenship | U.S.A. |
| Post Office Address | 2798 E. Amberwick Lane | | | | | | |
| Post Office Address | | | | | | | |
| City | Sandy | State | UT | ZIP | 84093 | Country | U.S.A. |

☒ Additional inventors are being named on the 2 supplemental Additional Inventor(s) sheet(s) PTO/SB/02A attached hereto

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| | | | | | | | |
|---|---------------|----------------------------|----|---|------------|-------------|--------|
| Name of Additional Joint Inventor, if any: | | | | <input type="checkbox"/> A petition has been filed for this unsigned inventor | | | |
| Given Name (first and middle [if any]) | | | | Family Name or Surname | | | |
| THOMAS J. | | | | KENNEDY | | | |
| Inventor's Signature | | | | Date | | | |
| Residence: City | WAUNAKEE | State | WI | Country | U.S.A. | Citizenship | U.S.A. |
| Post Office Address | | 5492 Kennedy Drive | | | | | |
| Post Office Address | | | | | | | |
| City | Wauakee | State | WI | ZIP | 53597 | Country | U.S.A. |
| Name of Additional Joint Inventor, if any: | | | | <input type="checkbox"/> A petition has been filed for this unsigned inventor | | | |
| Given Name (first and middle [if any]) | | | | Family Name or Surname | | | |
| PETER JAMES | | | | KNIGHT | | | |
| Inventor's Signature | | <i>pe knight</i> | | 10/20/99 | | Date | |
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| Post Office Address | | 1826 Gary Road | | | | | |
| Post Office Address | | | | | | | |
| City | Warren | State | NJ | ZIP | 08886 | Country | U.S.A. |
| Name of Additional Joint Inventor, if any: | | | | <input type="checkbox"/> A petition has been filed for this unsigned inventor | | | |
| Given Name (first and middle [if any]) | | | | Family Name or Surname | | | |
| DANIEL S. | | | | ROBINS | | | |
| Inventor's Signature | | | | Date | | | |
| Residence: City | New York | State | NY | Country | U.S.A. | Citizenship | U.S.A. |
| Post Office Address | | 77 E. 12th Street, Apt. 3B | | | | | |
| Post Office Address | | | | | | | |
| City | New York | State | NY | ZIP | 10003-5003 | Country | U.S.A. |

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
DECLARATION

ADDITIONAL INVENTOR(S) Supplemental Sheet

Page 2 of 2

| | | | | | | | |
|---|--|-----------------------|--|---|--|--------|--|
| Name of Additional Joint Inventor, if any: | | | | <input type="checkbox"/> A petition has been filed for this unsigned inventor | | | |
| Given Name (first and middle [if any]) | | | | Family Name or Surname | | | |
| ZEZHI, JESSE | | | | SHAO | | | |
| Inventor's Signature | | | | Date | | | |
| Residence: City | | BASKING RIDGE | | State | | NJ | |
| | | | | Country | | U.S.A. | |
| Post Office Address | | 68 Patriot Hill Drive | | | | | |
| Post Office Address | | | | | | | |
| City | | Basking Ridge | | State | | NJ | |
| | | | | ZIP | | 07920 | |
| | | | | Country | | U.S.A. | |
| Name of Additional Joint Inventor, if any: | | | | <input type="checkbox"/> A petition has been filed for this unsigned inventor | | | |
| Given Name (first and middle [if any]) | | | | Family Name or Surname | | | |
| | | | | | | | |
| Inventor's Signature | | | | Date | | | |
| Residence: City | | | | State | | | |
| | | | | Country | | | |
| Post Office Address | | | | | | | |
| Post Office Address | | | | | | | |
| City | | | | State | | | |
| | | | | ZIP | | | |
| | | | | Country | | | |
| Name of Additional Joint Inventor, if any: | | | | <input type="checkbox"/> A petition has been filed for this unsigned inventor | | | |
| Given Name (first and middle [if any]) | | | | Family Name or Surname | | | |
| | | | | | | | |
| Inventor's Signature | | | | Date | | | |
| Residence: City | | | | State | | | |
| | | | | Country | | | |
| Post Office Address | | | | | | | |
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DECLARATION

REGISTERED PRACTITIONER INFORMATION (Supplemental Sheet)

| Name | Registration Number | Name | Registration Number |
|--------------------------|---------------------|--------------------|---------------------|
| Carl W. Battle | 30731 | Gabriel P. Kralik | 34855 |
| Edwin P. Ching | 34090 | Susan Lee | 30653 |
| Eric S. Dicker | 31669 | Anita W. Magatti | 29825 |
| Cynthia L. Foulke | 32364 | Arthur Mann | 35598 |
| Robert A. Franks | 28605 | Edward H. Mazer | 27573 |
| Kenneth M. Goldman | 34174 | Jaye P. McLaughlin | 41211 |
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| Richard J. Grochala | 31518 | James R. Nelson | 27929 |
| Henry S. Hadad | 35888 | David B. Schram | 43096 |
| Thomas D. Hoffman | 28221 | Immac J. Thampoe | 36322 |
| Henry C. Jeanette | 30856 | Paul A. Thompson | 35385 |
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